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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/992,107 | 11/05/2001 | Michael J. Hope | 10173-072 | 7809 |

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| EXAMINER | |
|---|---|
| KISHORE, GOLLAMUDI S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1615 | 15 |

DATE MAILED: 07/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/992,107 | Applicant(s) Hope |
|---|---|---|
| | Examiner Gollamudi Kishore | Art Unit 1615 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *May 2, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *55-84* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *55-84* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *11*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

**The request for the extension of time, filing under 1.114 and the preliminary amendment all dated 5-2-03 are acknowledged.**

**Claims included in the prosecution are 55-84.**

### *Double Patenting*

**1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).**

**A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).**

**Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).**

**2. Claims 55-84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,139,871. Although the conflicting claims are not identical, they are not patentably distinct from each other because liposome sizes of 100-150 nm recited in the claims of said patent is included in instant 'greater than about 100 nm sizes; instant claims include the specific amounts of phospholipids recited in the claims of said patent.**

**This rejection is maintained in abeyance as per applicant's request.**

*Claim Rejections - 35 U.S.C. § 102*

**3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:**

> **A person shall be entitled to a patent unless --**
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

**4. Claims 55-56, 60-61, 67-71, 75, 76, and 82-84 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu (BBA, 1990).**

**Liu discloses liposomes of instant sizes(note the abstract, Materials and Methods, and results).**

**Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Liu does not teach compositions which are 1) pharmaceutically acceptable; in therapeutically effective amounts; 3) that are free of drug; 4) at least 68 % of the particles have the claimed diameter; 5) which mobilize more cholesterol than liposomes of 30 nm diameter. These arguments are not found to be persuasive. With regard to 1) and 2):- Liu teaches liposomes even without the radioactive tracer and therefore the composition appears to be pharmaceutically acceptable; applicant has not shown that to be otherwise. Applicant has also not shown that the amounts in Liu are not therapeutically effective amounts. Instant claims recite treatment and not cure and the treatment involves removal of cholesterol; applicant has not shown that Liu's compositions do not remove cholesterol. With regard to 3) :- instant claims recite 'free of**

**drug' and does not specify what drug it is. Liu's liposomes do not appear to contain any drug which is used for the treatment of vascular disease. Furthermore, although applicant recites claim 55 with the limitation, 'free of drug', in the dependent claim 61 recites lipoproteins and globulins which could be construed as drugs; according to page 12 of the specification, lipoproteins accept cholesterol and therefore, are drugs. With regard to 4) :- on page 350, col. 1 Liu clearly teaches 120 nm diameter and the examiner is unable to find at this location 200 nm diameter as argued by applicant. With regard to applicant's arguments based on Ostro's reference that sonication will produce liposomes in the 25-50 meter range, the examiner points out that since Liu teaches 120 nm, a proper comparison will be Liu's procedure (under the same conditions) with instant method and not with Ostro's. This argument is also not valid since according to page 9 of instant specification, one of the methods of production of instant liposomes is by sonication (line 33 et seq.). The reference still reads on instant claims and as suggested in the interview, applicant must amend the claims reciting 'empty liposomes' and with the language 'consisting essentially of' and include further limitations which will enable applicant to overcome Liu.**

**5. Claims 55-56, 60, 62, 64-68, 70-71, 75, 77, and 79-83 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 470 437.**

**EP teaches unilamellar liposomes having an average diameter of 100 nm containing phosphatidylcholine for the treatment of atherosclerosis (note pages 10, 11, 15 and 16 of the English translation).**

**Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Hager does not teach at least 68 % of the liposomes have a mean diameter of 125 +30 nm. This argument is not found to be persuasive since 'at least 68 % indicates that the value can be between 68 and 100 and the reference teaches 129 nm in example 3; applicant has not shown that this value does not fall within the claimed range. With regard to the Gaussian distribution argued by applicant, the examiner points out that instant claims do not recite this limitation. With regard to applicant's arguments that the DNA marker, propidium iodide in Example 3 of Hager, the examiner points out instant independent claims exclude a drug and not a marker; furthermore, many DNA alkylating agents are toxic and by themselves are mutagenic and carcinogenic and yet they are used in cancer therapy in humans (The molecular basis of cancer is cited in this context; note pages 262-283). On this basis, one can conclude that this compound is pharmaceutically acceptable. In addition, the examiner points out that the references teaches limited number of examples of liposomes the majority of them are without a marker meeting the requirements of 102 rejection and one of ordinary skill in the art will not to attach the marker if the desired goal is only to treat atherosclerosis in humans and not for diagnostic purposes since the reference through examples shows how to make the liposomes of different sizes.**

*Claim Rejections - 35 U.S.C. § 103*

**6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:**

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

**7. Claims 55-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP cited above.**

**As pointed out above, EP teaches the use of empty liposomes of different diameters for the treatment of atherosclerosis. EP does not provide specific examples for the treatment of atherosclerosis. It would however, been obvious to an artisan to use liposomes for the treatment of atherosclerosis based on the teachings of EP. Although in Example 3 where the liposomes of claimed sizes are prepared, the reference indicates the attachment of a DNA marker to the liposomes, it is deemed obvious to one of ordinary skill in the art not to attach the marker if the desired goal is only to treat atherosclerosis in humans and not for diagnostic purposes since the reference through examples shows how to make the liposomes of different sizes. EP does not also specifically teach instant protocol of administration. In the absence of showing unexpected results, these parameters are deemed to be obvious parameters manipulated by an artisan to obtain the best possible results.**

**Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that Hager does not teach at least 68 % of the**

**liposomes have a mean diameter of 125 +30 nm. This argument is not found to be persuasive since 'at least 68 % indicates that the value can be between 68 and 100 and the reference teaches 129 nm in example 3; applicant has not shown that this value does not fall within the claimed range. With regard to the Gaussian distribution argued by applicant, the examiner points out that instant claims do not recite this limitation. With regard to applicant's arguments that the DNA marker, propidium iodide in Example 3 of Hager, the examiner points out again that one of ordinary skill in the art will not to attach the marker if the desired goal is only to treat atherosclerosis in humans and not for diagnostic purposes since the reference through examples shows how to make the liposomes of different sizes. The examiner also points out that many DNA alkylating agents are toxic and by themselves are mutagenic and carcinogenic and yet they are used in cancer therapy in humans (The molecular basis of cancer is cited in this context; note pages 262-283).**

**8. Claims 55-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams (BBA, 875, pp., 183-194, 1986) in combination with EP cited above.**

**Williams teaches a method of administration of liposomes and liposomes together with plasma (contains lipoproteins) and the alterations in lipid metabolism and the regression of experimental atherosclerosis as a result of such an administration (note the Materials and Methods section and the discussion). What is lacking in Williams is the teachings of the sizes of liposomes. However, the methodology disclosed on pages 184 and 185 indicated that sonicated liposomes were passed through a 0.22 microns filter and**

**therefore, it would have been obvious to one of ordinary skill in the art that the liposomes would contain liposomes of instant sizes. Even assuming that the sizes in Williams are different from instant sizes, one of ordinary skill in the art would be motivated to use liposomes larger than 50 nm with a reasonable expectation of success since EP which deals with the treatment of same disease state advocates the use of liposomes of instant sizes.**

**Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Williams also does not suggest using a population of liposomes falling within the claimed Gaussian distribution. This argument is not found to be persuasive since as pointed out above, instant claims do not recite this limitation. With regard to applicant's arguments that Williams shows that increase in LDL after the administration of SUVs and applicant points out to Fig. 2A of Williams in this regard. A close examination of this figure appear to indicate that even the corresponding controls have the same peak height and therefore, the examiner is unable to determine whether there is a statistically significant difference between values for the controls and the liposomes. Irrespective of this, the rejection is based on the combination and EP teaches instant sizes.**

**9. Claims 55-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams (1984 or 1986) in view of Liu.**

**Williams (1984) teaches the administration of liposomes for treating atherosclerosis, but does not teach the sizes (pages 418-423). This parameter however, if different from instant invention, is deemed to be an obvious parameter manipulated by an artisan to obtain the best possible results. Instant liposome sizes are also deemed to be obvious to one of ordinary skill in the art in view of Liu's teachings that SUVs of about 120 nm have greater circulation time.**

**Williams (1986) disclose a method of removal of serum cholesterol using liposomes (note the abstract, Introduction, Materials and Methods and Discussion, last paragraph in particular). Although on page 185, col. 1, Williams discloses the use of 0.22 mm filter, he does not specifically teach instant sizes.**

**Liu teaches that small liposomes (<200 nm) remain in circulation for a longer periods (note page 348, col. 2, Results on page 350, col. 1).**

**To prepare liposomes of Williams (1984 or 1986) having sizes within the claimed range would have been obvious to one of ordinary skill in the art since liposomes of those sizes are able to survive the circulation system for longer periods (and hence their enhanced cholesterol removal effect) as taught by Liu. The protocol of administration is deemed to be an obvious parameter manipulated by an artisan.**

**Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Williams, and Liu have already been addressed above.**

**10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.**

**The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.**

**If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.**

**Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].**

**All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.**

**Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.**

**Gollamudi S. Kishore, Ph. D**

**Primary Examiner**

**Group 1600**

***gsk***

**July 2, 2003**